UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/017,324	12/15/2001	Christopher Thomas Walsh	55046 (70207)	8192

21874 7590 08/18/2005

EDWARDS & ANGELL, LLP
P.O. BOX 55874
BOSTON, MA 02205

EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 08/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/017,324	WALSH ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53,55 and 59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-53,55 and 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1656.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 11, 2005 has been entered.

Claims 1-53, 55, and 59 are pending.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 4, 7, 10, and 12-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) Claims 4 and 37 contain the phrase "weakly-nucleophilic", which renders the claims indefinite for the reasons. The phrase is a relative term and one of ordinary skill in the art would not be able ascertain the metes and bound of the claimed invention set forth in the prior Office action mailed 1/30/04 and 1/13/05.

In response to the above rejection, applicants continue to traverse the rejection on the ground that the phrase is well known in the art and submitted several pages of a textbook by McMurry to support their allegation.

Applicants' arguments filed 7/11/05 have been fully considered, but they are found unpersuasive. The examiner disagrees. Clearly, McMurry order the various nucleophiles relative to their rate of reaction in S_{n2} reaction, and teaches that the nucleophilicity of a chemical compound is related to various factors that include the ionization constant for the nucleophile and the steric environment of nucleophilic center. It should be noted that their is no absolute scale in which various solvent are known as strong and weak nucleophile, but one of ordinary skill in the art can ascertain the nucleophilicity of a reagent relative to other reagents, e.g., in a series of primary alcohols or amines. Solvent such as DMSO, DMF, acetone, and acetonitrile are known as "polar aprotic solvents".

(b) The phrase "hydrocarbon group" in claims 10, and 28-33 renders the claims indefinite for the reasons set forth in the prior Office actions mailed 1/30/04 and 1/13/05.

In response to the above rejection, applicants continue to traverse the rejection on the ground that the phrase is defined in the specification at page 16, first paragraph.

Applicants' arguments filed 7/11/05 have been fully considered, but they are found unpersuasive. The definition at page 16, first paragraph, is repugnant to one of ordinary skill in the art. A "hydrocarbon group" as the term means in the art and the English language is a group of carbon and hydrogen atoms connected to one another by covalent bonds. No heteroatom such as oxygen, nitrogen or sulfur can be included in the term. While it is true that applicants are entitled to be their own lexicographer, they are not entitle to give a well known phrase in the art and the English language a new meaning.

(c) The phrase "N-C_2-C_6alkanoylC_2-C_6aminoalkyl" in claims 12-33 renders the claims indefinite for the reasons set forth in the prior Office actions mailed 1/30/04 and 1/13/05.

In response to the above rejection, applicants continue to traverse the rejection on the ground that the phrase is a standard IUPAC nomenclature.

Applicants' arguments filed 7/11/05 have been fully considered, but they are found unpersuasive. The examiner disagrees. For example the appropriate chemical name for Ac-NH-CH_2-CH_2-SH is 2-N-acetyl-2-aminoethan-1-thiol. The general formula above does not identify the position of the sulfur atom and the position of the amino group has to be identified before the atom. The formula does not conform to the IUPAC nomenclature as alleged by applicants, and therefore, the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-53, 55 and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the prior Office actions mailed 1/30/04 and 1/13/05.

In response to the above rejection, applicants traverse the rejection on the bases that the entire specification should be used to determine whether or not the written description requirement is met, and not just the example.

Applicants' arguments filed 7/11/05 have been fully considered, but they are found unpersuasive. The examiner agrees that the entire specification should be considered for compliance with the written description requirement. The claims are directed to the cyclization of a large genus encompassing different classes of organic compounds using any thioesterase domain from any polyketide synthase gene cluster or any non-ribosomal peptide synthase. The specification provides example of the cyclization reaction using tyrocidine A homologus series of polypeptide catalyzed by the thioesterase domain from the tyrocidine synthase. The novel finding of the data presented in Table 1 at page 41 is that the excised thioesterase domain of tyrocidine synthase catalyzes the cyclization of an exogenously formed substrate, and the thiesterase domain has substrate specificity, as it requires D-Phe (R-configuration at the chiral center) in position number one of the substrate. No thioesterase is disclosed that is able to catalyze any linear chemical compound having the formulas in claims 10, 12, 14, 18, 22, 28, 42, 47, 50, and 59. No other thioesterase domain is disclosed as excised and functional from any other source other than tyrocidine synthase or capable to catalyze the cyclization of a peptide comprising an amino acid residue at the N-terminus have a chiral center with S-configuration. It should be noted that peptide substrate constrained number of conformation which the can assume in aqueous solutions due to the restricted rotation around the peptide bond. In contrast, if the linker is a polyether or saturated carbon chain, the conformation of such molecules is expected to be highly flexible. The specification failed to teach a structure activity relationship among these molecules, and which thioesterase domain can be excised in active and functional form and is expected to catalyze a specific structural formula. Clearly, one of ordinary skill in the art would come to the conclusion that applicant did not have possession of the claimed invention at the time the application was filed from reading the entire specification specification.

Claims 34-53, and 55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons set forth in the prior Office actions mailed 1/30/04 and 1/13/05.

In response to the above rejection, applicants traverse the rejection and argue that the claims are not directed to a method wherein the elongation is repeated indefinitely. The elongation step is repeated only until the substrate of sufficient length to undergo macrocyclization.

Applicants' arguments filed 7/11/05 have been fully considered, but they are found unpersuasive. Claims 34-41 are directed to a method wherein initially a substrate is homodimerize or heterodimerize having any structure comprising a thioester at the C-terminus and a nucleophile at the other end using any thioesterase domain from any polyketide synthase or non-ribosomal peptide synthase, which produces a second elongated substrate suitable for cyclization. Claims 42-53 and 55 limits the structure of the substrate to contain (R)-2-amino-, hydroxy-, or thio-2-benzylpropunic acid moiety. The application contains no single example of such a method. The specification fails to provide any example of the homologus or heterologus dimerization reactions. The dimerization reaction is always in competition with the cyclization and the hydrolysis reactions. While the intermolecular cyclyzation appears to be sufficiently competitive with the hydrolysis reaction, see Figure 2 (d), the intramolecular dimerization is not expected to be competitive with the hydrolysis reaction between pH 6-8. Furthermore, the heterodimerization if it takes place at all, would be expected to give multiple products at best. Clearly, the specification have failed to teach a structure activity relation ship between the structure of the thioesterase and the substrate to use to carry out a dimerization reaction followed by cyclization reaction. Thus, written descriptions in the specification fails to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and therefore, the claims remain rejected.

Claims 1-53, 55, and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the prior Office action mailed 1/30/04 and 1/13/05.

In response to the above rejection, applicants continue to argue that the specification id fully in compliance with the enablement requirement.

Applicants' arguments filed 7/11/05 have been fully considered, but they are found unpersuasive. Enablement requires a disclosure sufficient to allow a person of skill in the art to practice the full scope of the claimed invention without undue experimentation. The previous Office action sets out a *prima facie* case of non-enablement, explaining by sound scientific reasoning why a person of ordinary skill in the art would doubt that the guidance of the specification would enable practice of the full scope of the claimed invention without undue experimentation. Applicants have presented no evidence or, indeed, any arguments to establish the adequacy of the disclosure to enable the scope of the instant claims. Applicants merely assert that the disclosure of two thioesterases domain from non-ribosmal peptide synthase enable the cyclization and dimerization of the broad genus compounds claimed. Applicants make no effort to explain why they consider the disclosure of two non-ribosmal peptide synthase thiesterases cyclizing a limited number of their native substrates and closely

related homolog thereof to be enabling with respect to all cyclization and dimerization reactions encompassed by the claims. Applicants should note that no single dimerization reaction has been exemplified or known in the prior art under the conditions thought by applicants. Applicants exemplify neither dimerization nor cyclization reaction catalyzed by thioesterase domain from a polyketide synthase gene cluster. Conclusory statements unsupported by evidence or scientific reasoning are insufficient to overcome the *prima facie* case of non-enablement set out in the previous Office action.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-8 and 11 are rejected under 35 U.S.C. 102(a) as being anticipated by Trauger *et al.* (Nature Sept. 2000, 407, 215-218), for the reasons set forth in the prior Office action mailed 1/30/04 and 1/13/05.

In response to the above rejection, applicants file a copy Rule 131 Declaration, and argue that Trauger *et al.* is not a prior art against the claims of the instant application.

Applicants' arguments and the Rule 131 declaration filed 7/11/05 have been fully considered, but they are found unpersuasive. Section 715 (II), (G), states:

> "Where applicant has clearly admitted on the record that subject matter relied on in the reference is prior art. In this case, that subject matter may be used as a basis for rejecting his or her claims and may not be overcome by an affidavit or declaration under **37 CFR 1.131**. *In re Hellsund*, 474 F.2d 1307, 177 USPQ 170 (CCPA 1973); *In re Garfinkel*, 437 F.2d 1000, 168 USPQ 659 (CCPA 1971); *In re Blout*, 333 F.2d 928, 142 USPQ 173 (CCPA 1964); *In re Lopresti*, 333 F.2d 932, 142 USPQ 177 (CCPA 1964)."

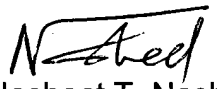
Trauger *et al.* is an admitted prior art in the specification, and support the enablement requirement, see page 11, second paragraph. At page 27 of applicants' response to the previous Office action, it states "Trauger *et al.* state that the PKS systems can produce new polyketide and peptide. Applicants have known at the time they filed the instant application of the teaching of Trauger *et al.* and used it to support the instant application. Thus, the claims remain rejected.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Nashaat T. Nashed, Ph. D.
Primary Examiner
Art Unit 1656